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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	9

DATE MAILED: 06/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/756,687	CURRY ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 28-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21 and 28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The election with traverse filed April 29, 2002 in Paper No. 7 is acknowledged and has been entered.

2. The amendment filed on April 29, 2002 in Paper No. 7 is acknowledged and has been entered. Claims 22-27 have been canceled. Claims 1-3 and 13 have been amended. Claims 28-33 have been added.

3. Claims 1-21 and 28-33 are pending in the application and are currently under continued prosecution.

Election/Restrictions

4. Upon reconsideration of the claims, the restriction requirement set forth in the Office action mailed March 27, 2002 (Paper No. 6) is hereby vacated. Accordingly, pending claims 1-21 and 28-33 have been examined.

Applicants' grounds of traversal of the restriction requirement are noted, but are moot in view of the fact that the restriction requirement has been vacated.

Specification

5. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of improperly demarcated trademarks include Chremophor™ (page 47), American Type Tissue Collection™ (page 53), and Promega™ (page 56).

Appropriate corrections are required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate

symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

6. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion. See pages 76-79 of the specification for examples of such disclosures.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-21 and 28-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,290,712-B1 in view of US Patent Nos. 4,436,727-A, 4,912,094-A, 5,149,527-A, 5,579,554-A, 5,756,541-A, 5,747,475-A, 5,770,619-A, 5,929,105-A, 5,990,149-A, 6,071,944-A, and 6,149,671-A and Momma, et al (*Cancer Research* **58**: 5425-5431, 1998), Fischer, et al (*Journal of Photochemistry and Photobiology B* **43**: 27-33, 1998), Karrer, et al (*Dtsch Med Wochenschr* **122**: 1111-1114; abstract only), Lapes, et al (*Journal of Photochemistry and Photobiology B* **36**: 205-207, 1996), and van Hillegersberg, et al (*British Journal of Cancer* **71**: 733-737, 1995).

US Patent No. 6,290,712-B1 teaches a method for treating a neoplasm, including a malignant tumor, in a human or other animal, which comprises administering to the subject a chromophore (i.e., photosensitizer) and an immunoadjuvant and then irradiating the tumor at a wavelength sufficient to induce the destruction of the tumor and to stimulate the immune system so that further neoplastic cellular proliferation in the subject is prevented or inhibited (abstract). For clarification, the term "malignant" is used to describe a tumor that is anaplastic, invasive, and metastatic; that is, it has primitive cellular growth characterized by a lack of differentiation, it moves into and destroys surrounding tissue, and it spreads to other parts of the body. Therefore, a characteristic of all malignant tumors is the capacity to metastasize. In this regard, US Patent No. 6,290,712-B1 teaches, "it is an object of this invention to improve the treatment of neoplasms by combining photodynamic and immunologic therapies in such a way as to cause immediate neoplastic cellular destruction while concomitantly stimulating the self-immunological defense system against proliferation of residual or metastatic cells" (column 5, lines 24-29). While '712 exemplifies the use of a particular photosensitizer, namely indocyanine green, other suitable photosensitizers are disclosed (column 7, lines 36-60); specifically, '712 teaches that upon absorption of a particular wavelength of light, suitable photosensitizers should have the ability "to create thermal energy, to evolve singlet oxygen and other active molecules, or to be toxic in their own right" (lines 40-43). '712 exemplifies the use of modified chitosan as the immunoadjuvant, but discloses that other immunoadjuvants that non-specifically stimulate the immune system can be also be used, including those comprising a component of bacterial cell walls (column 9, lines 10-15). '712 teaches that both the photosensitizer and the immunoadjuvant can be administered intratumorally (for example, column 15, lines 10-20), but also discloses that the photosensitizer can be administered systemically (column 2, lines 26-28). '712 teaches that their method has several advantages over conventional and unconventional treatment modalities, but the "combination of sensitizer and immune-stimulation adjuvant is the key" (column 5, lines 63-65). '712 concludes, the "most significant advantage is a combined acute and chronic tumor destruction" (column 5, lines 65 and 66). '712 demonstrates the utility of

the invention to treat both primary and metastatic tumors, the latter of which arose as metastases of a primary tumor, in Figures 1 and 2 and Figures 3 and 4, respectively. '712 also demonstrates the use of the invention to prevent the development of metastases in Figure 5.

However, US Patent No. 6,290,712-B1 does not explicitly disclose that a suitable photosensitizer is a "green porphyrin" or benzoporphyrin derivative (BPD), namely BPD-MA, EA6, or B3. In addition, '712 does not explicitly teach that the amount of photosensitizer administered to the subject can range between 0.05 and 10 mg/kg of body weight or that the subject can be treated with the photosensitizer and irradiated before the immunoadjuvant is administered. '712 does not explicitly disclose that the immunoadjuvant can comprise mycobacterial cell wall extracts and/or lipid A from a gram-negative bacterium, namely de-3-O-acylated lipid A. Also, '712 does not explicitly disclose that the subject may have undergone previous therapeutic treatment for cancer or that the immunoadjuvant can be administered systemically. '712 does not teach that the photodynamic therapy regimen can be repeated 1-3 times, nor does '712 teach the repeated administration of the immunoadjuvant at an interval of about two weeks. Finally, '712 does not disclose that the method can comprise an additional step in which the subject is irradiated at a wavelength that improves the penetration of absorbed light before the subject is irradiated at the wavelength at which the photosensitizer absorbs light.

US Patent No. 6,149,671-A teaches a method for treating a neoplasm, such as a malignant tumor, in humans and other animals. The method comprises selecting a chromophore, i.e., a photosensitizer, and an immunoadjuvant, introduces both into a neoplasm to obtain a conditioned neoplasm, and irradiating the conditioned neoplasm to destroy the neoplasm and produce fragmented neoplastic tissue to stimulate host defenses against the neoplasm. '671 demonstrates the utility of the invention to treat both primary and metastatic tumors, the latter of which arose as metastases of a primary tumor. '671 demonstrates the utility of the invention to treat both primary and metastatic tumors, the latter of which arose as metastases of a primary tumor, in

Figures 1 and 2 and Figures 3 and 4, respectively. '671 also demonstrates the use of the invention to prevent the development of metastases in Figure 5.

US Patent No. 5,747,475-A teaches a method for treating a neoplasm, such as a malignant tumor, in humans and other animals. The method comprises selecting a chromophore, i.e., a photosensitizer, and an immunoadjuvant, introduces both into a neoplasm to obtain a conditioned neoplasm, and irradiating the conditioned neoplasm to destroy the neoplasm and produce fragmented neoplastic tissue to stimulate host defenses against the neoplasm. '475 demonstrates the utility of the invention to treat both primary and metastatic tumors, the latter of which arose as metastases of a primary tumor. '475 demonstrates the utility of the invention to treat both primary and metastatic tumors, the latter of which arose as metastases of a primary tumor, in Figures 1 and 2 and Figures 3 and 4, respectively. '475 also demonstrates the use of the invention to prevent the development of metastases in Figure 5.

US Patent No. 5,770,619-A teaches a method for administering photodynamic therapy to a subject in order to effectively destroy a solid tumor (abstract; claims). '619 teaches that the method comprises administering to a subject either locally or systemically a benzoporphyrin derivative (BPD), namely BPD-MA and then irradiating at least a portion of the subject at a wavelength that is sufficient to photoactivate BPD-MA (column 3, lines 20-54). '619 discloses an advantage is gained in using BPD, because "BPD also has demonstrated a higher affinity for tumor tissue, including leukemic cells, than for normal non-malignant cells" (column 1, lines 59-61). '619 also discloses that the photosensitizer can be administered intravenously for systemic delivery or topically for localized delivery (column 5, lines 59-65) at doses that range from 0.5 to 2.0 mg/kg of body weight (Figure 1). However, with regard to the appropriate and effective dose, '619 teaches:

> This invention is the conduct of effective PDT [photodynamic therapy] more safely and with fewer adverse effects because the post injection interval is much shorter and doses of both the photosensitive agent and light are halved. In contrast, previously it was thought that the photosensitizer initially distributed nonselectively throughout the body and that it took several hours to days for the photosensitizer to accumulate selectively in the target tissue. It was thought that selective distribution occurred gradually, with a considerable amount of exchange between the target tissue and the pool of circulating

> photosensitizer molecules. Thus, it was considered essential to delay post injection light treatment by several hours to days (column 6, lines 53-64).
>
> These two surprising results encouraged testing of early, lower dose illumination in tumor treatment with PDT (i.e., before photosensitizers permeate skin or other normal tissue). Experimental evidence (presented below) in mice indicates the inventive method is safe and effective (column 7, lines 30-34).

US Patent No. 5,990,149-A teaches the synthesis of another suitable benzoporphyrin derivative, namely B3, which is a potent photosensitizer and can therefore substitute for BPD-MA. '149 specifically discloses, "BPD-MA was found to have particularly useful properties for PDT and is currently in clinical development. However, there remains a need for additional specific forms of photoactive agents which expand the repertoire of photoactive compounds for the variety of indications to which PDT is applied" (column 1, lines 62-66).

US Patent No. 5,929,105-A also teaches a method for photodynamic therapy of cancer, wherein benzoporphyrin derivatives, namely the isomers A-EA6 and B-EA6 are administered to the subject (claims). '105 teaches that A-EA6 has a stronger immunomodulatory effect than BPD-MA (column 13, lines 34-36). Furthermore, '105 discloses that B-EA6 does not accumulate in non-tumor tissue, whereas BPD-MA accumulates in the skin within the first three hours following administration of the photosensitizers to the subject (column 7, lines 56-58). Moreover, as compared to BPD-MA, '105 discloses an additional advantage in using EA6, which is that B-EA6 clears more rapidly from all normal tissues while specifically accumulating in the tumors, which is of benefit because B-EA6 will have less non-specific toxicity and can therefore be more safely administered to the subject (column 7, lines 41-45 and 59-61; column 10, lines 18-20).

US Patent No. 5,149,527-A teaches that an immunopotentiating protocol, which causes the death or regression of developing tumors in subjects in whom previously received antitumor therapy resulted in the successful destruction of the tumor or parts thereof, wherein an immunoadjuvant is administered to the subject at a time after the previous therapy when formation of tumor-specific macrophages has occurred as the result of the primary tumor's destruction (abstract). '527 discloses the following:

> The invention is directed to protocols for effecting tumor regression and/or necrosis in animal subjects. In particular, it involves pretreatment of the tumor with a tumor destroying protocol, such as a chemotherapeutic agent, radiation, or hyperthermia, for a time and in a manner effective to cause the formation of tumor-specific cytotoxic macrophages and other tumor infiltrating effector cells and then to administer a quantity of immunopotentiator specific for these macrophages which effectively results in lysis of the tumor. Essentially, the tumor-destructive protocol that precedes treatment with immunopotentiator is used to provide "vaccination in situ" (column 2, lines 25-38).

'527 discloses that localized antitumor therapy, e.g., photodynamic therapy, is "usually effective to produce at least partial destruction of the neoplasm" (page 3, lines 24-26). Furthermore, '527 teaches that a wide variety of immunoadjuvants can be used in the protocol provided that the agent is capable of stimulating macrophages and can be administered locally or systemically by intravenous injection (Figure 1; column 4, lines 42-56; column 5, lines 15-23). While '527 does not explicitly teach that immunoadjuvants comprising modified chitosan can be used to stimulate tumor-destructive macrophages, it does disclose that mycobacterial cell wall extracts and detoxified lipopolysaccharide (e.g., monophosphoryl lipid A) are suitable (Figure 1).

US Patent No. 5,579,554-A teaches an effective means for treating cancer, which comprises administering to the subject in need of therapy an immunoadjuvant composed of modified mycobacterial cell wall extract (abstract). '554 discloses, "[t]he present invention is also effective in treating various cancers that occur in both humans and animals. The cancers can be primary or metastatic" (column 3, lines 42-45). The advantage that '554 provides is that the immunoadjuvant is effective but does not need to be suspended in oil and therefore its use precludes the development of granulomas in subjects treated with immunoadjuvants comprising oil (column 4, lines 5-9; column 2, lines 39-42). '554 teaches the following:

> The present invention relates to an aqueous suspension of a mycobacterial cell wall extract that is effective in treating the immune system in animals and humans. The aqueous suspension can optionally have glycosaminoglycans, such as hyaluronic acid, as a component. The present invention is an aqueous preparation of modified bacterial cell walls that does not contain any oil or oil-like substances. Because there is no oil in the aqueous suspension of the mycobacterial cell wall extract that comprises the present invention, the unwanted side effects that are present in the cell wall preparations that are in the prior art are eliminated. The aqueous suspension of the mycobacterial cell wall extract is capable of stimulating the immune system of an animal or human, thereby causing the body to neutralize or abort an infection or retard or eliminate the growth of a cancer (column 1, lines 8-15).

Furthermore, to explain the beneficial effects of the immunoadjuvants, '554 discloses:

> Whether large complex molecules like peptidoglycans or lipopolysaccharides or simple molecules such as muramyl dipeptide are used, the common pathway points to macrophage activation as the mechanism of adjuvant activity. The stimulation of macrophages by adjuvants results in increased antigen uptake, enhanced cytotoxicity, phagocytosis, hydrogen peroxide production, arachidonic acid metabolism, enzyme degranulation, and the synthesis and release of polypeptide monokines. The polypeptide monokines play an important role because they possess potent biological properties for various cells. To date, these monokines include interleukin 1, alpha interferon, tumor necrosis factor (cachectin), and colony-stimulating factors. Each monokine can, in turn, trigger other cells to produce biologically active cytokines (column 2, lines 15-29).

In addition, '554 teaches that the aqueous mycobacterial cell wall extract can be injected directly into the tumor or it can be given systemically (column 5, lines 14-24). '554 teaches multiple injections of liposome encapsulated MDP, a small component of the mycobacterial cell wall, has been reported to have diminished the number of lung and lymph node metastases; and '554 discloses repeated injections of the immunoadjuvants rarely cause the development of hypersensitivity.

Thus, at the time the invention was made, it was well known in the art that lipid A is the lipid fraction of lipopolysaccharide (LPS), which is ordinarily obtained from Gram-negative bacteria. Furthermore, numerous studies had demonstrated that most or all of the potent immunoadjuvant activity of Gram-negative bacterial endotoxin (i.e., LPS) resides in the lipid A moiety of LPS. While LPS or the lipid A fraction thereof is too toxic to be used as an adjuvant for treatment of humans and other animals, modified lipid A, such as monophosphoryl lipid A was known to be less toxic than the unphosphorylated lipid and was therefore commonly used as an non-specific immunostimulant at the time the invention was made. In this regard, US Patent No. 4,912,094-A teaches that modified lipopolysaccharides, particularly de-3-O-acylated monophosphoryl lipid A and de-3-O-acylated diphosphoryl lipid A retain a high level of immunostimulating capacity but have the advantage of being considerably less endotoxic than naturally occurring lipopolysaccharide (abstract).

US Patent No. 4,436,727-A also teaches an immunoadjuvant comprised of a detoxified endotoxin (i.e., LPS) product, which when combined with mycobacterial cell wall skeleton extracts, can be used as an effective means for treating a subject

diagnosed with cancer (abstract). '727 teaches that the combination of immunoadjuvants is more effective than the detoxified endotoxin alone (column 6, lines 30-45). '727 teaches multiple injections of the immunoadjuvant, up to five, can be made at intervals of at least one week to impart immunotherapy in a subject having an immunogenic tumor.

US Patent No. 5,756,541-A teaches that a regimen of photodynamic therapy using "green porphyrins" or benzoporphyrin derivatives, such as MA, can be repeated two times to provide an improvement in the result of the therapy.

US Patent No. 6,071,944-A teaches a method for treatment of malignant melanoma, which also comprises administering to the subject a photosensitizer and then irradiating the subject at a wavelength at which the photosensitizer absorbs light. '944 discloses that the efficacy of photodynamic therapy can be hampered if lesions are pigmented, which is often the case with highly metastatic melanoma, because the pigmented tumor cells are less responsive; the lack of response attributed to optic filtering by melanin granules within the cells (column As a solution to the problem, '944 teaches that pretreatment of pigmented tumors with high peak power light (such as 1064 nm light) enhances their susceptibility to conventional photodynamic therapy (column). Therefore, '944 teaches that photodynamic therapy is more efficacious when the subject is irradiated at a wavelength that improves penetration of the wavelength of light at which the photosensitizer absorbs.

Momma, et al teach the use of a "green porphyrin" to effectively control primary tumors and distant metastases of the primary tumor. Momma, et al teach the combination of a surgical approach and photodynamic therapy using a liposomal benzoporphyrin derivative monoacid ring A. Momma, et al teaches that the combination of surgery and photodynamic therapy is more effective than either modality alone.

Fischer, et al teach that photodynamic therapy with Photofrin II™ and mTHPC can be used effectively suppress hematogenous dissemination of micrometastases.

van Hillegersberg, et al teach that adjuvant intraoperative photodynamic therapy diminished the rate of local recurrence of a tumor and prevented the development, or diminished metastases in the lymph nodes of treated animals.

Karrer, et al demonstrate that photodynamic therapy can be used effectively in a clinical setting to completely eliminate metastases in a subject.

Lapes, et al demonstrate that photodynamic therapy can be used effectively treat a subject diagnosed with metastases, if not to completely destroy the subject's metastases.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, in view of the teachings of US Patents Nos. 4,436,727-A, 4,912,094-A, 5,149,527-A, 5,579,554-A, 5,747,475-A, 5,770,619-A, 5,929,105-A, 5,990,149-A, 6,071,944-A, and 6,149,671-A and Momma, et al, Fischer, et al, Karrer, et al, Lapes, et al and van Hillegersberg, et al, to improve the method of US Patent No. 6,290,712-B1 by deriving a method for treating, preventing, or inhibiting primary or metastatic tumors or the development thereof in a subject, said method comprising administering to the subject a green porphyrin photosensitizer, namely BPD-MA or B3, or more particularly EA6, and an immunoadjuvant comprising mycobacterial cell wall extract (MCWE) and/or a derivative of bacterial lipopolysaccharide (LPS) lipid A and irradiating the subject with light of a wavelength absorbed by said photosensitizer, wherein said photosensitizer can be administered intravenously or intratumorally before irradiation of the subject at a dose ranging from 0.05 to 10 mg/kg body weight, wherein said irradiation can be localized to the tumors, and wherein said immunoadjuvant can be administered systemically and administered repeatedly, one to five times, at intervals of at least one week, and wherein the regimen of photodynamic therapy can be repeated up to two times.

US Patent No. 6,290,712-B1 and US Patent Nos. 6,149,671-A and 5,747,475-A teach an effective method for treating a malignant tumor in a human or other animal, which comprises administering to the subject a photosensitizer, namely indocyanine green or another suitable photosensitizers that upon absorption of a particular wavelength of light, has the ability to create thermal energy, to evolve singlet oxygen and other active molecules, or to be toxic in their own right, and an immunoadjuvant, namely an immunoadjuvant derived from chitosan, and then irradiating the tumor at a wavelength sufficient to induce at least the partial destruction of the tumor and to

thereby stimulate the immune system in the presence of the immunoadjuvant so that further destruction of the tumor will result and also further neoplastic cellular proliferation in the subject will be prevented or inhibited. In view of the teachings of US Patent No. 5,770,619-A, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute BPD-MA for the photosensitizer of '712, because '619 discloses an advantage is gained in using BPD, namely BPD has a higher affinity for tumor tissue than for normal non-malignant cells; and besides, '712 teaches that BPD is a suitable photosensitizer since BPD has the ability to create thermal energy, to evolve singlet oxygen and other active molecules, or to be toxic in their own right upon absorption of a particular wavelength of light. Moreover, '619 teaches that lower dosages of BPD can be administered to subjects while still achieving therapeutic benefit, which is an advantageous since photosensitizers are toxic compounds and therefore limiting the necessary dosage is desirable. According to the teachings of US Patent No. 5,990,149-A B3, which is also potent BPD photosensitizer can substitute for BPD-MA. However, it view of the teachings of US Patent No. 5,929,105-A, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the green porphyrins A-EA6 or B-EA6 for the photosensitizer of '712, because '105 teaches that A-EA6 has a stronger immunomodulatory effect than BPD-MA and B-EA6 does not accumulate in non-tumor tissue, whereas BPD-MA accumulates in the skin within the first three hours following administration of the photosensitizers to the subject. Moreover, as compared to BPD-MA, '105 discloses an additional advantage in using EA6, which is that B-EA6 clears more rapidly from all normal tissues while specifically accumulating in the tumors, which is of benefit because B-EA6 will have less non-specific toxicity and can therefore be more safely administered to the subject.

In view of the teachings of US Patent No. 5,149,527-A, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute an adjuvant that is disclosed as being capable of stimulating macrophages, namely a detoxified derivative of mycobacterial cell wall extract, such as that taught by US Patent No. 5,579,554-A, or a detoxified lipid A derivative, such as that taught by US

Patent No. 4,912,094-A, for the immunoadjuvant of '712, because '527 discloses that an immunoadjuvant that is administered to the subject at a time after the previous successful therapy, when formation of tumor-specific macrophages is occurring as the result of the primary tumor's destruction, causes the death or regression of developing tumors in subjects. While '527 does not explicitly teach that immunoadjuvants comprising modified chitosan, such as the immunoadjuvant of '712, can be used to stimulate tumor-destructive macrophages; however, '527 does disclose that mycobacterial cell wall extracts and detoxified lipopolysaccharide are suitable. US Patent No. 5,579,554-A teaches an effective immunoadjuvant composed of modified mycobacterial cell wall extract (MCWE), which stimulates macrophages and which can be used to treat a patient diagnosed with a primary or metastatic (i.e., secondary) tumor. According to the disclosure of '554, the advantage of using MCWE is that the immunoadjuvant can be administered systemically or locally in an aqueous form; therefore its use precludes the development of granulomas in subjects, which is an adverse effect of treating subjects with immunoadjuvant comprising oil. Furthermore, '554 teaches the immunoadjuvant can be administered repeatedly up to five times at intervals of at least one week without frequently causing hypersensitivity to diminish the number of metastases to the lung and lymph nodes. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the modified MCWE of '554 for the immunoadjuvant of '712. Alternatively, based upon the teachings of '527, it also would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the modified LPS, particularly de-3-O-acylated monophosphoryl lipid A of '554, for the immunoadjuvant of '712, because '527 indicates that modified lipid A is also capable of stimulating macrophages and de-3-O-acylated diphosphoryl lipid A retains a high level of immunostimulating capacity, but have the advantage of being considerably less endotoxic than other naturally occurring and modified LPS derivatives. Finally, in view of US Patent No. 4,436,727-A, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute a combination of modified BCWE and modified LPS, particularly de-3-O-acylated monophosphoryl lipid A

of '554, for the immunoadjuvant of '712, because '727 teaches an immunoadjuvant comprised of combination of a detoxified LPS product and detoxified mycobacterial cell wall skeleton extract can be used as an effective means for treating a subject diagnosed with cancer, but moreover '727 teaches that the combination of immunoadjuvants is more effective than one of immunoadjuvants alone.

Furthermore, in view of US Patent No. 6,071,944-A, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to further modify the improved method of US Patent No. 6,290,712-B1 to the claimed method can further comprise an additional irradiation with light of a wavelength that improves penetration of the absorbed light before irradiating the subject at the wavelength absorbed by the photosensitizer, because '944 teaches that photodynamic therapy is more efficacious when the subject is first irradiated at a wavelength that improves penetration of the wavelength of light at which the photosensitizer absorbs, especially if the tumor cells are pigmented.

In view of US Patent No. 5,756,541-A, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to repeat the photodynamic therapy regimen more than once to improve the outcome of the treatment.

In view of the teachings of Momma, et al, it would have been *prima facie* obvious to one of ordinary skill in the art to combine surgery and photodynamic therapy to treat a subject diagnosed with either a primary tumor or metastases, because Momma, et al teach that the combination of surgery and photodynamic therapy is more effective than either approach alone.

In view of the teachings of US Patents Nos. 4,436,727-A, 4,912,094-A, 5,149,527-A, 5,579,554-A, 5,747,475-A, 5,756,541-A, 5,770,619-A, 5,929,105-A, 5,990,149-A, 6,071,944-A and 6,149,671-A, Momma, et al, Fischer, et al, Karrer, et al, Lapes, et al, and van Hillegersberg, et al, one of ordinary skill in the art, at the time the invention was made, would have been motivated to improve the method of US Patent No. 6,290,712-B1 to more effectively treat primary or metastatic tumors, the latter of which arose by the metastasis of a primary tumor, and moreover, because there was a

long-felt need at the time for more efficacious therapeutic means for treating, preventing, or inhibiting primary and secondary cancers in humans and other animals. Additionally, one of ordinary skill in the art would have been motivated to have done so, because Fischer, et al teach photodynamic therapy can suppress the hematogenous dissemination of micrometastatic cells, because van Hillegersberg, et al teach that adjuvant intraoperative photodynamic therapy diminished the rate of local recurrence of a tumor and prevented the development, or diminished metastases in the lymph nodes of treated animals, and finally because Karrer, et al and Lapes, et al demonstrate that photodynamic therapy can be used effectively in a clinical setting to completely eliminate metastases in a subject.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR § 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR § 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR § 3.73(b).

10. Claims 1-17 and 28-33 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application No. 09/556,833. Although the conflicting claims are not identical, they are not patentably distinct from each other because given the subject matter of claims 1-16 of copending Application No. 09/556,833, the subject matter of claims 1-21 and 28-33 of the instant application would be obvious to one of ordinary skill in the art. Moreover, the claimed methods are essentially the same, and the only differences would be obvious to the artisan of ordinary skill. For example, given the claims of copending Application No. 09/556,833, it would be obvious to use the claimed invention to treat a malignant tumor in a subject, since the claims of copending Application No. 09/556,833 are drawn to a method for treating a tumor that results from metastasis.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

11. No claims are allowed.

12. The art made of record and the prior art made of record, but not relied upon is considered pertinent to Applicants' disclosure. Krosl, et al teaches the enhancement of the effect of photodynamic therapy upon tumor cells by an immunostimulatory agent. Korbelik, et al (*Cancer Res* 1996) teaches the activity of lymphoid cells is essential to the prevention of the recurrence of tumors following photodynamic therapy. Korbelik, et al (*J Photochem Photobiol B* **44**: 151-158, 1998; cited by Applicants) teaches that the effect of photodynamic therapy in treating tumors can be enhanced by adjuvant treatment with an immunoadjuvant. Korbelik, et al (Br J Cancer 75: 202-207, 1997; cited by Applicants) teaches adjuvant therapy using an immunostimulatory agent has a synergistic effect on tumor cures achieved by photodynamic therapy. Korbelik, et al (*Cancer Lett* 1999) demonstrates that sustained activation of immune cells is essential

for the maintenance of long-term control of tumors treated using photodynamic therapy. Korbelik, et al (*Photochem Photobiol* 2001) teach the amplification of the antitumor effects of photodynamic therapy by adjuvant immunoadjuvant therapy.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

S Rawlings
STEPHEN RAWLINGS

slr
June 5, 2003